IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application of:	Denise L. Faustman	**ON APPEAL**
Serial No.:	09/913,664	ART UNIT: 1651
Filed:	August 17, 2001	EXAMINER: V. Afremova
Entitled:	METHOD FOR INHIBITING TRANSPLANT REJECTION	

Atty. Docket No.: DLF-002.1P US

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REPLY BRIEF

Sir:

Pursuant to 37 C.F.R. §41.41, Appellant submits this Reply Brief responding to issues raised in the Examiner's Answer issued January 10, 2007 in the above-referenced patent application.

This Reply Brief is filed simultaneously with Appellants' Request for an Oral Hearing and the filing fees specified under 37 C.F.R. §41.20(b)(3) (check no. 7404).

The Commissioner is hereby authorized to charge any additional fees required in connection with the filing of this paper or to credit any overpayment to Deposit Account No. 50-0268.

REMARKS

Inadequacy of the Primary Reference, Civin, US 5,081,030

Appellant asserts that the final rejections maintained by the Examiner, which are requested to be reviewed in this appeal, rely particularly on an oversimplification and overinterpretation of the primary Civin reference (U.S. 5,081,030), which oversimplification and overinterpretation are necessary in order to stretch that reference to meet the features of Appellant's invention. On page 4 of the Examiner's Answer, the Civin reference is characterized as follows:

> "US 5,081,030 discloses a method for transplantation bone marrow cells wherein the method comprises step of treating a viable donor tissue with enzyme chymopapain (col. 11, lines 30-35), step of transplanting the treated viable donor tissue into host mammal (col. 11, line 45) and step maintaining the treated viable donor tissue in the host mammal (col. 11, line 57)." (See, Examiner's Answer, page 4.)

Reading now the features of Appellant's claims on appeal, it is seen that the Examiner's characterization of Civin does not equal Appellant's claimed invention: Whereas the Examiner raises "step of treating a viable donor tissue with enzyme chymopapain", Appellant's Claim 1 calls for "treating viable donor tissue with an enzyme *effective for temporarily ablating MHC Class I antigens from the donor tissue*"; whereas the Examiner raises "step of transplanting the treated viable donor tissue into host mammal", Appellant's Claim 1 calls for "transplanting said treated, viable donor tissue into said host mammal *before MHC Class I antigens are re-expressed* on the surface of said donor tissue"; and whereas the Examiner raises "step maintaining the treated viable donor tissue in the host mammal" (citing a line in the Civin reference merely saying that treated or control cells "were engrafted"), Appellant's Claim 1 calls for maintaining said viable donor tissue in said host.

There is obviously a concept missing from the Civin teaching which is central to Appellant's invention, namely, that of removing MHC Class I surface antigens from donor tissue, using the treated donor tissue in transplantation before such surface antigens can be re-expressed on the surface of the tissue, and maintaining the transplant in the host, where the re-expressing MHC Class I antigens can be taken by the host immune system as "self" antigens and tolerated. Reference to MHC Class I antigen presentation on donor tissue is absent from Civin, as is its role in transplant rejection or any hint of an idea as to how MHC Class I surface antigens might be altered to avoid their effect in transplantation.

The Civin reference is not a reference concerned with inhibiting transplant rejection. It is a reference teaching a method for positive selection of immature (progenitor) hematopoietic bone marrow cells using a stage-specific cell surface antigen, MY-10, for affinity separation, after which

cells are released from the affinity matrix by enzymatic cleavage of the cell surface structure (CD34) that includes the MY-10 epitope. See, Civin, col. 2, lines 8-20.

The fact that the appearance of MY-10 on cells is stage-specific, i.e., that it appears on progenitor cells but not on mature cells, is explained more fully in an earlier Civin patent, US 4,714,680, which is cited several times in the Civin reference relied on by the Examiner. (See, e.g., Civin, US 5,081,030 at col. 2, line 21; col. 6, line 4. A copy of US 4,714,680 is appended at Tab A.) MY-10-positive cells comprise less than 5% of normal bone marrow cells and less than 1% of normal peripheral blood cells. (See, Civin, US 4,714,680 at col. 4, lines 34-46.) Moreover, epitope MY-10 is no longer expressed (along with the CD34 surface protein that contains it) on the surface of mature cells. (See, Civin, US 4,714,680 at col. 4, lines 29-33.)

The Civin reference relied on by the Examiner, therefore, pertains to positive selection of cells on the basis of a surface antigen that appears only on progenitor cells and not on mature, fully differentiated cells.

Appellant's main point with respect to Civin is that, in failing even to mention MHC Class I removal as a concept, it is inadequate to anticipate or render obvious the methods of the appealed claims. Appellant's second point with respect to Civin is that Civin not only DOES NOT make any reference to ablation of MHC Class I surface antigens, it CAN NOT be interpreted to contain a teaching of eliminating MHC Class I surface antigens, for the reason that Civin teaches the positive selection of MY-10-positive progenitor cells, which are precisely cells that have little or no MHC Class I expression (at that stage of their differentiation). Accordingly, Civin *cannot* be interpreted as communicating to the person of ordinary skill in the art the most important features of Appellant's claims, namely, temporarily ablating MHC Class I molecules from the surface of donor tissue intended for transplant and then using the treated tissues for transplant before rejection-mediating MHC Class I surface antigens reappear.

The Examiner's answer to Appellant's first point is to find in Civin a reference to cells intended for bone marrow graft, the use of a cleaving enzyme, and a background discussion of Graft versus Host Disease (GVHD); however, the cells are not the cells contemplated by the present invention, the use of enzyme for release of cells from an affinity matrix does not accomplish what is required by Appellant's claims, and the discussion of GVHD does not bring the Civin reference into the art of transplant rejection – GVHD is characterized by T lymphocyte attack from the graft on tissues of the host (see, e.g., Civin, US 5,081,030 at col. 1, lines 29-30; col. 2, lines 1-7), whereas transplant rejection is characterized by the host's immune system attack on donor tissue (see, e.g., Itescu, Evidence Appendix, Tab B of Appellant's Brief, page 4, para. 2). The common elements found

by the Examiner to compare with Appellant's invention do not communicate the essence of Appellant's invention or allow the person of ordinary skill in the art even to begin to inhibit transplant rejection in a manner akin to the method of the appealed claims.

The Examiner's answer to Appellant's second point against the Civin reference is to argue that because Civin deals with isolation of adult bone marrow cells, they are cells that express HLA Class I. The Examiner apparently confuses "adult" with "mature" cells, the former referring to the age of the donor, the latter referring to the developmental stage of the cell. It is not disputable that the Civin process is directed at collecting stem cells or progenitor cells from bone marrow and excluding from the collection mature, or fully differentiated cells. (Civin, US 5,081,030 at col. 5, lines 59-67.) The Examiner argues that the authorities cited by Appellant to show the understanding of those of ordinary skill in the art that progenitor cells are MHC Class I-negative are distinguishable as relating only to embryonic stem cells and pointing out that the Civin reference refers to adult (as opposed to embryonic) donors. However, the Itescu publication (Tab B of Appellant's Brief) is a review article, and it includes several statements showing that embryonic stem cells and adult stem cells exhibit the same features. For example, the Itescu article includes the following statement:

> "Stem cells obtained from embryonic ***or adult*** sources differ from other somatic cells in that they express very low levels of HLA molecules on their cell surfaces." (Itescu, Evidence Appendix, Tab B of Appellant's Brief, at page 2, para. 5.) (emphasis added)

Finally, the Examiner argues that the sorted progenitor cells of Civin, being "nucleated cells of adult tissue", exhibit MHC Class I antigen complexes on their surfaces, citing the statement of Abbas et al. from page 78 of Cellular and Molecular Immunology that "Class I molecules are constitutively expressed on virtually all nucleated cells." (Examiner's Answer, page 11.) However, although it is not readily apparent from the excerpt supplied by the Examiner, this teaching of Abbas et al. obviously refers to fully differentiated cells. Indeed, the same statement appears on page 1 (line 25) of Appellant's application. The point of Appellant's citations is to underscore the understanding of those of ordinary skill in the art that the cells that are the target of the Civin separation process (progenitor bone marrow cells) are not fully differentiated blood cells exhibiting an abundance of MHC Class I; and because of that fact of Nature, the person of ordinary skill would not be informed by the Civin reference of any method involving cleavage of MHC Class I from the surface of cells or of any need to do so in a transplant context or of any expectation of inhibiting transplant rejection by collecting donor cells according to the method of Civin.

On page 11 of the Examiner's Answer, the Examiner points to Examples 10 and 11 of Civin (US 5,081,030 at col. 11) as showing the engraftment of unselected, mature rat bone marrow cells that

have been treated with chymopapain. However, it is expressly stated in Example 11 that the bone marrow graft was made in "syngeneic rats" (col. 11, line 45), meaning that the rats were receiving bone marrow genetically identical to their own, and thus no immune rejection would be expected (the rats and the donor bone marrow being MHC-identical). Those experiments were to show reconstitution of hematopoiesis in irradiated rats, not to test rejection of transplanted tissue.

Civin is relied on to show all of the steps of Appellant's method, but it is seen that it is competent to show none of them. The common elements between the Civin cell selection process and Appellant's claims are not enough to make the Civin reference relevant to the claimed invention let alone to render it anticipated within the meaning of 35 U.S.C. §102 or, in combination with the secondary and tertiary references, obvious within the meaning of 35 U.S.C. §103. For the foregoing reasons, the rejections of the appealed claims relying in any way on Civin are in error and should be reversed by this Board.

Inadequacy of the Secondary/Tertiary References

GALATI

With respect to Appellant's argument that the Galati reference is in no way related to transplantation and is simply a laboratory method for removing and quantitating the level of MHC Class I expression on the surface of cells, the Examiner argues,

> "Galati . . . also teaches that MHC Class I molecules are integral membrane glycoproteins expressed on most nucleated cells . . ." (Examiner's Answer, page 11.)

Appellant does not dispute that MHC Class I molecules are expressed on the surface of (differentiated) nucleated cells. The Galati reference, however, does not provide the essential features of Appellant's invention that are not disclosed in Civin, namely, the treatment of donor tissue to temporarily ablate surface MHC Class I molecules prior to transplantation, followed by use of the donor tissue for transplantation before re-expression of the MHC Class I molecules occurs. None of the Examiner's citations (particularly not Civin and not Galati) recognizes the role of MHC Class I antigens in transplant rejection, and more importantly none of the references proposes a method relying on initial MHC Class I ablation and depending on MHC Class I re-expression for inhibition of transplant rejection. These concepts are absent from any configuration of the prior art as relied on by the Examiner.

LEE

With respect to Appellant's argument that the Lee reference (US 5,670,358) actually teaches away from treating cells with papain or chymopapain to avoid damage to the cells during the process of digesting the connective tissue to release the cells, the Examiner argues,

> "[Lee] is relied upon to demonstrate that the presently claimed hepatocytes and islets cells useful for transplantation are prepared by enzymatic treatment with chymopapain and papain." (Examiner's Answer, page 13.)

Appellant asserts that what the Examiner argues is the teaching of Lee is exactly what the Lee reference expressly teaches to avoid. The Examiner would have the Board understand Lee as teaching that hepatocytes and/or islet cells can be prepared for transplantation by contacting the cells directly with papain or chymopapain. However, according to Lee,

> "An exemplary process of the present invention includes enzymatically **digesting connective tissue** by providing an enzyme composition containing papain or chymopapain . . . in an amount sufficient to hydrolyze connective tissue and dissociate desired viable cells from such tissue . . . **It is essential to halt** or at least substantially slow down the **enzymatic activity** in the medium containing the isolated viable cells **as soon as possible after the cells are dissociated from the tissue** in order **to preserve the cell integrity**. This is accomplished by preventing excessive digestion." (Lee, column 2, lines 21-33.) (emphasis added)

Therefore, in contrast to the Examiner's argument, Lee does not teach the preparation of hepatocytes/islet cells for transplant by treatment with papain or chymopapain. Rather, Lee teaches digesting connective tissue with papain or chymopapain and avoiding contacting the liberated hepatocytes/islet cells with either of these enzymes, as exposure to them can destroy cell viability. In addition, MHC class I antigens are not mentioned in Lee, nor is there any mention of intentionally cleaving MHC class I antigen complexes from the cell surface for any reason.

BROWNLEE

With respect to the Brownlee reference, the Examiner states,

> "[Brownlee] is relied upon to demonstrate that the cells treated with papain (but not transfected . . .) re-express the MHC class I surface molecules . . .". (Examiner's Answer, page 13.) (emphasis in original)

However, the Examiner has not addressed the main distinction Appellant points out between the present invention and the reference combination including Brownlee, namely, that Brownlee fails

to recognize the role of the re-emergence of MHC Class I antigens in the education of the host immune system to tolerate the presence and propagation of the donor cell population. Appellant's claims require that the ability to re-express MHC Class I antigens after ablation is maintained in the enzyme-treated donor cells; by contrast, Brownlee teaches the permanent genetic alteration of the donor cells so as to lose their ability to produce MHC Class I antigens permanently. Thus, addition of Brownlee to the reference combination does not bring the aggregate teaching of the prior art closer to suggesting Applicant's invention.

STONE

With respect to the Stone et al. reference, again the Examiner has not addressed Appellant's distinctions with respect to the present invention, simply stating, instead,

> "Stone et al. is mainly relied upon for the teaching that glycosidase such as or alpha-galactosidase is known to remove alpha-gal epitopes from xenograft tissues in order to alter or to reduce immune response of host recipient upon transplantation." (Examiner's Answer, paragraph bridging pages 14 and 15.)

It is acknowledged that the Stone reference is relied on mainly as stated above by the Examiner, however Appellant points out that the particular xenograft of Stone is non-viable and is not subject to hyperacute rejection by the host. Therefore, the Stone teaching is incompetent for the purpose the Examiner cites it. In other words, Stone has no application to "a method of *inhibiting rejection* . . . of donor tissue . . . which is transplanted into [a] host mammal," as is claimed in the present invention, since the killed cartilage plugs of Stone *are not donor tissue subject to rejection.* Likewise, since Stone is not concerned with and makes no mention of ablation of MHC Class I antigens from donor tissue, it does not cure the multiple failures of the Civin, Galati, Lee and Brownlee references to suggest even the critical first step of Appellant's invention.

CONCLUSION

In the Examiner's Answer of January 10, 2007, the Examiner has either restated the reasoning for the rejections raised in the final Office Action without specifically addressing the points raised by Appellant in the Brief on Appeal or has refuted known scientific facts, including that adult progenitor cells are regarded as essentially MHC Class I-negative, by mis-citing the Abbas et al. text for a statement inapplicable to progenitor cells or emphasizing portions of references for points that are refuted elsewhere in the same reference.

Appellants strenuously submit that although the present invention calls for the use of donor cells, and that the cells are contacted with enzymes such as papain, and that cells being contacted by

enzymes is illustrated in the references (for various effects unrelated to transplantation), these slight points of contact with the terms of the appealed claims are not sufficient to demonstrate that the present invention was in the hands of the art at the time Appellant's application was filed, nor was the present invention obvious to a person of ordinary skill apprised of the art represented by any combination of Civin, Galati, Brownlee, Lee, and/or Stone.

For the foregoing reasons, it is clear that no teaching or suggestion of the Appellant's invention exists in the prior art, and reversal of all rejections is therefore respectfully solicited.

Respectfully submitted,

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